

Investigation of factors affecting recurrence in locally advanced stage cervical cancer

Recurrence in cervical cancer

Belma Gözde Özdemir, Fazıl Avcı, Ahmet Bilgi, Çetin Çelik
Department of Gynecology And Obstetrics, Faculty of Medicine, Selçuk University, Konya, Turkey

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Abstract

Aim: Cervical cancer has a high risk of morbidity and mortality and is also a preventable gynecological cancer. In this study, we aimed to evaluate the prognostic factors of recurrence development in patients operated on for cervical cancer in our clinic.

Materials and Methods: In this retrospective study, patients diagnosed with LACC (II-IVA 2018 FIGO) at Selçuk University Faculty of Medicine between December 2010 and April 2022 were included.

Results: Patients were divided into two subgroups according to age, smoking status, tumor size, and location (in millimeters) on magnetic resonance imaging, histological type, staging type, pelvic and paraaortic lymph node positivity, radiotherapy modalities, pelvic and pelviparaaortic application, treatment method, and response rates.

There was a statistically significant difference in stage (stages 2, 3, and 4), response to adjuvant treatment, disease-free survival, and overall survival between the two groups.

Discussion: The study demonstrated that disease stage and response to adjuvant treatment are significant prognostic factors affecting recurrence and survival in locally advanced cervical cancer.

Keywords

cervical cancer, MRI, recurrence, staging

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Corresponding Author: Belma Gözde Özdemir, Department of Gynecology And Obstetrics, Faculty of Medicine, Selçuk University, Konya, Turkey.

E-mail: gzdgrgn35@gmail.com P: +90 530 936 94 59

Corresponding Author ORCID ID: <https://orcid.org/0000-0002-7025-4087>

Other Authors ORCID ID: Fazıl Avcı, <https://orcid.org/0000-0002-9244-9168> · Ahmet Bilgi, <https://orcid.org/0000-0001-8682-1739>

Çetin Çelik, <https://orcid.org/0000-0001-6165-5092>

This study was approved by the Ethics Committee of Selçuk University (Date: 2025-01-14, No: E922332)

Introduction

According to 2018 GLOBOCAN data, cervical cancer ranks fourth after cancer and cancer-related causes worldwide, with 570,000 cases and 311,000 fatalities. Other malignancies include breast, colorectal, and lung cancer. In terms of deaths, it comes in fourth. Locally advanced cervical cancer (LACC) (stages IB2-IVA/IB3-IVA, respectively) according to the International Federation of Gynecology and Obstetrics (FIGO) 2009/2018 [1]. This definition is essential since it helps determine and grade treatment options, prognosis, survival, persistence, and recurrence. In this context, numerous parameters are considered [2]. Concurrent chemotherapy and pelvic radiation are used to treat locally advanced cervical cancer. New treatment approaches have to be developed, though, because of the dismal survival rates.

Stage, nodal status, tumor volume, lymphovascular space invasion (LVSI), depth of cervical stromal invasion, and, to a lesser extent, histological type and grade are the primary prognostic variables that impact survival [3,4]. Our objective was to assess variables predictive of recurrence.

Materials and Methods

Patients at Selçuk University Faculty of Medicine diagnosed with LACC (II-IVA, 2018 FIGO) between December 2010 and April 2022 were included in this retrospective cohort analysis. Ninety cases in all were assessed, comprising 20 with recurrence (group 2) and 70 without recurrence (group 1). A total of 90 patients diagnosed with locally advanced cervical cancer were screened and subsequently classified into two groups based on the presence or absence of recurrence. Patients were included if they had histopathologically confirmed cervical cancer, were categorized as FIGO 2018 stage II-IVA, had pretreatment MRI imaging available, and had completed definitive chemoradiotherapy or radiotherapy. Patients were excluded if they lacked necessary imaging or pathology data, had incomplete treatment, had a follow-up duration shorter than six months, or had a history of prior pelvic radiotherapy. Recurrence was defined as radiologic evidence of new or progressive lesions identified on MRI, supported by corresponding clinical findings. In cases where radiologic findings were inconclusive, recurrence was confirmed through biopsy. Clinical and radiological variables collected for analysis included patient age and smoking status, tumor diameter measured on axial T2-weighted MRI sequences, histological type, pelvic and para-aortic lymph node involvement—where lymph nodes with a short-axis diameter of at least 10 mm were considered positive—along with the staging method used, the radiotherapy modality and treatment protocol administered, and the individual response to therapy categorized as complete response, partial regression, or progression.

Age, smoking, MR size (based on 20 mm and 50 mm limits), histologic type (squamous, adeno, and other), staging (surgical imaging), pelvic lymph node, paraaortic lymph node, radiotherapy modality (pelvic, pelvic-paraaortic lymph nodes), treatment protocols (radiotherapy, chemoradiotherapy, and brachytherapy), treatment response (progression, regression, and complete response), recurrence ranges (local, extensive, regional, and extensive), disease-free survival, and overall

survival are all included in the clinicopathology classification. Care modalities (chemotherapy, chemotherapy + palliative, radiotherapy, surgery + chemotherapy, palliative radiotherapy, supportive care) and metastatic site (lung, liver, bone, multiple) are the criteria used in this classification for recurrence. Clinical and radiological variables collected for analysis included patient age and smoking status, tumor diameter measured on axial T2-weighted MRI sequences, histological type, pelvic and para-aortic lymph node involvement—where lymph nodes with a short-axis diameter of at least 10 mm were considered positive—along with the staging method used, the radiotherapy modality and treatment protocol administered, and the individual response to therapy categorized as complete response, partial regression, or progression. All patients were treated with either concurrent chemoradiotherapy followed by brachytherapy or radiotherapy alone in cases where chemotherapy was contraindicated. Chemotherapy consisted of weekly cisplatin at a dose of 40 mg/m², while brachytherapy was applied using standard intracavitary techniques. Patients were monitored every three months during the first two years and every six months thereafter. MRI examinations were routinely performed between three and six months after treatment completion and annually in the subsequent follow-up period.

Statistical Analysis

All statistical analyses were performed using SPSS version 21. The normality of continuous variables was evaluated using the Kolmogorov–Smirnov test. Parametric variables were analyzed with the Student's t-test, whereas non-parametric variables were assessed using the Mann–Whitney U test. Categorical variables were compared using the Chi-Square test or Fisher's Exact Test where appropriate. Survival analyses were conducted using the Kaplan–Meier method, and differences between survival curves were assessed with the log-rank test. A p-value of < 0.05 was considered statistically significant. For all comparative analyses presented in the supplementary tables, the corresponding statistical tests used are indicated directly below each supplementary table. Categorical variables were analyzed using Chi-Square or Fisher's Exact Test, while continuous variables were assessed with Student's t-test or the Mann–Whitney U test, depending on distribution characteristics. This standardized presentation aims to improve clarity and reproducibility.

Ethical Approval

This study was approved by the Ethics Committee of Selçuk University (Date: 2025-01-14, No: E922332).

Results

Age, smoking status, size, and location on magnetic resonance imaging (in millimeters), histological type, staging type, positivity for pelvic and paraaortic lymph nodes, radiotherapy modalities, pelvic and pelviparaaortic application, treatment modality, response rates to treatment, location and time of recurrence, DFS, and OS rates were used to divide patients into two subgroups. After that, recurrence cases were covered individually. It shows the localization site, metastatic location, and subsequent therapy regimens. The tabular presentation of the data is presented in summarized form as supplementary

material.

There was no statistically significant difference in the mean ages of groups 1 and 2 (60.4 ± 12.1 and 56.0 ± 10.4 years, respectively). Smoking, MRI lesion diameter (mean 2 cm and 5 cm), histological type, staging method (extraperitoneal or MRI), number of pelvic and para-aortic lymph nodes, radiotherapy method (pelvic and pelvic-para-aortic), and treatment protocol did not differ significantly between the two groups. In terms of stage (stages 2, 3, and 4), response to adjuvant treatment, disease-free survival, and overall survival, the two groups differed statistically significantly (Figures 1 and 2). Thirteen (65%) of the recurrences were local, four (20%) were local + remote, and three (15%) were far. The most frequent distant recurrence sites were the bone in 2 cases and the lung in 3. Three patients had lung recurrences, two had bone recurrences, one had liver recurrence, and one had multiple metastases. At ten, twelve, and fifteen months, the modal recurrences were local, local + distant, and distant, respectively. Seven patients received chemotherapy (CT); five received surgery and CT; three received CT and palliative radiotherapy (RT); one received palliative RT; and four received supportive treatment.

Discussion

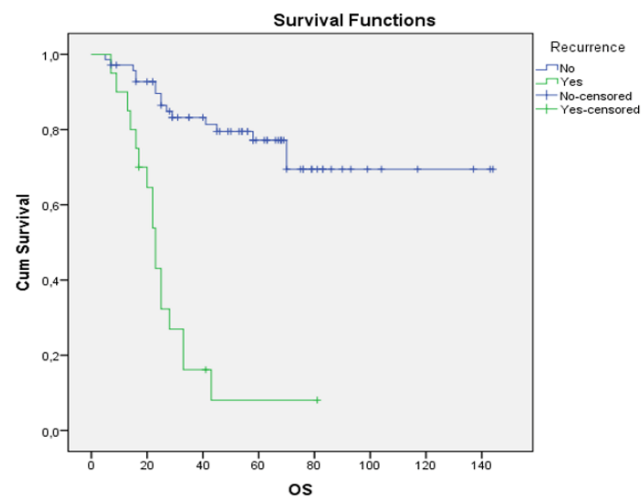


Figure 1. OS analysis according to recurrence

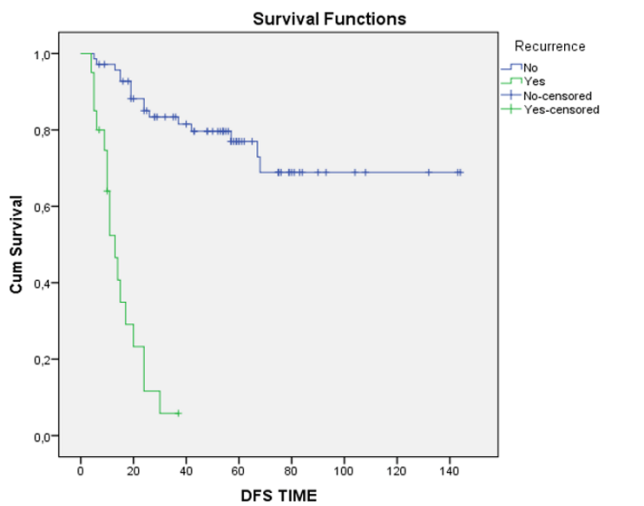


Figure 2. DFS analysis according to recurrence

A study suggests that pelvic lymph node size and radiation resistance are poor prognostic factors in patients with pelvic lymph node positivity. This finding may aid in risk categorization of this patient population [5]. In this study, no significant difference was observed between the groups in pelvic or paraaortic lymph node positivity; however, significant differences were observed in stage, treatment response, DFS, and OS. This, when considered alongside the findings of Pinto et al., suggests that recurrence depends not only on lymph node involvement but also on the tumor’s biological behavior in advanced stages and the nature of the response to treatment. Especially in advanced-stage patients (Stages III–IV), increasing primary tumor burden, depth of stromal invasion, and the extent of micrometastatic spread appear to be additional factors explaining the development of recurrence. Although disease stage showed a statistically significant difference between the recurrence and non-recurrence groups, stage alone does not fully explain why only a subset of advanced-stage patients develop recurrence. The literature suggests that additional biological factors, such as lymphovascular space invasion (LVSI), depth of stromal invasion, tumor volumetric burden, and the extent of micrometastatic dissemination, contribute significantly to recurrence risk. Moreover, proliferative activity, as reflected by immunohistochemical staining intensity, tumor necrosis, and diffusion-based imaging parameters such as apparent diffusion coefficient (ADC) values, has been associated with more aggressive tumor behavior and reduced sensitivity to chemoradiotherapy. In line with these findings, our study demonstrated that treatment response—remarkably incomplete regression—was among the most influential determinants of recurrence. This indicates that recurrence is multifactorial and reflects the interplay between anatomical extent, treatment resistance, and underlying tumor biology rather than stage alone.

In this study, as in ours, lymph nodes were considered. The prognostic significance of the presence, number, and location of lymph node metastases (pelvic, pelvic plus para-aortic) was evaluated by comparing survival and recurrence. It was assessed as a significant negative factor for postoperative recurrence in patients with locally recurrent or persistent cervical cancer treated with single or combined lymphadenectomy [6,7]. Both literature indicators emphasize the need to consider lymph node metastasis in clinical decision-making, underscoring its role as a key determinant in treatment planning and follow-up strategies. When considered alongside the findings of our study, higher stage and treatment nonresponse in patients experiencing recurrence appear to outweigh the clinical impact of lymph node involvement. However, this does not diminish the prognostic value of lymph node metastasis; instead, it suggests that nodal involvement and treatment response should be evaluated together in larger patient groups.

Important issues regarding therapeutic approaches and pain management have been highlighted. This is demonstrated by the fact that fewer opioids are given to relieve pelvic pain compared to chemotherapy or targeted therapy [8]. The study observed that pain management was a significant clinical challenge in some patients who developed recurrence due to advanced tumor burden, local spread, and the presence of metastatic

foci. The fact that chemotherapy, palliative radiotherapy, or supportive care was administered to the recurrence group indicates that pain and other symptoms significantly worsen in these patients, making palliative approaches necessary. It was emphasized that opioid use is required in most cases for pelvic cancer pain, but may not be sufficient alone due to the frequent occurrence of a neuropathic component. Given the complex nature of pain experienced in recurrent local or local-distant disease, the need for multimodal analgesic strategies becomes clear.

In patients with locally advanced cervical squamous cell carcinoma who received chemoradiotherapy, a modeling was planned based on clinical factors and hyaluronic type, and the value of whole-tumor tissue analysis of the diffusion coefficient (ADC) map was examined [9]. It may be a new indicator for predicting cervical cancer recurrence, measuring hemoglobin, albumin, lymphocytes, and platelets. This is a marker scale with a normogram [10].

Although no significant differences were found between the groups in MRI mass size and measurements in our study, as shown in the literature, tissue characteristics and tumor volumetric size are essential determinants of recurrence risk. Therefore, it is clear that risk estimation based solely on size or lymph node status is inadequate, and imaging techniques must be supplemented with more advanced biomarkers. Given that aggressive biological behavior can increase the likelihood of recurrence by diminishing the response to radiotherapy or chemoradiotherapy, incorporating ADC-based analyses into clinical decision-making may be a promising approach.

Although the advanced disease stage was more common among patients who experienced recurrence, the stage alone does not sufficiently differentiate which individuals are most likely to recur. Our findings indicate that the most potent determinant of recurrence was the degree of response to primary treatment, particularly to chemoradiotherapy. Patients who failed to achieve a complete response or demonstrated < 30% or moderate partial regression were markedly more likely to recur. This suggests that treatment resistance—reflecting underlying tumor biology—plays a more prominent role than anatomical stage in predicting recurrence. Factors known to contribute to poor response, such as high tumor burden, extensive stromal invasion, lymphovascular space invasion (LVSI), intratumoral necrosis, and diffusion-restricted tumor tissue, have been shown in previous studies to underlie this resistance. Therefore, in our cohort, the interplay between treatment response and aggressive tumor characteristics appears to be a more decisive predictor of recurrence than stage alone.

The Korean Gynecologic Oncologic Group KGOG-1024 risk assessment model can also be used to determine whether patients will benefit from adjuvant systemic therapy following chemoradiotherapy by calculating the side effect profile [11]. Some studies have shown that tumor necrosis on magnetic resonance imaging at the time of diagnosis, uterine corpus infiltration, and mesorectal infiltration are essential [12]. According to 13 studies, chemotherapy increased 5-year survival by 6% compared with the same radiation alone. Two studies using chemotherapy after chemoradiation showed a greater survival advantage. A significant survival advantage

was observed in the study group receiving both platinum-based and non-platinum-based chemoradiation, despite no significant differences in chemotherapy, radiation dosage, or timing. Chemotherapy also reduced local and distant progression and recurrence and improved disease-free survival (DFS). There is evidence of a difference in the magnitude of the survival advantage according to tumor stage, but not among other patient groups. It is essential to remember hematologic and genitourinary side effects [13].

In subsequent studies, chemotherapy was shown to increase overall survival (OS) and DFS compared with RT alone, particularly in patients with stage IIIB disease [14,15]. The factors affecting recurrence in locally advanced cervical cancer, as reported in the literature, are very complex and cannot be explained solely by tumor stage or lymph node status. Studies show that pelvic and para-aortic lymph node metastasis is a determinant of survival and recurrence, and the number and distribution of metastatic nodes significantly influence prognosis. Furthermore, chemoradiotherapy has been shown to offer a survival advantage over radiotherapy alone, reduce the risk of local and distant disease progression, and provide more significant benefits, particularly in advanced stages. While neoadjuvant chemotherapy offers a potential option for reducing tumor burden and improving surgical eligibility, unclear patient selection criteria limit its clinical application. Furthermore, the fact that surgical treatment is associated with poorer survival outcomes, even in early-stage patients using minimally invasive techniques, strengthens the rationale for preferring chemoradiotherapy as the primary treatment for locally advanced cases. Furthermore, biological and systemic markers, such as ADC-based tumor texture analysis and HALP (Hemoglobin, Albumin, Lymphocyte, and Platelet score), have become increasingly crucial for predicting recurrence, and tumor microstructural characteristics and the patient's inflammatory and nutritional status are critical factors influencing treatment response. Furthermore, the need for pain management and palliative care is reported to increase in patients with recurrence, and local and bone metastases, in particular, are reported to lead to a high symptom burden. Taken together, these findings suggest that our study should evaluate the role of tumor size in upstaging and low treatment response rates in patients with recurrence. All these data point to the need for personalized treatment strategies for locally advanced cervical cancer, closer monitoring of high-risk patients, and the integration of new prognostic models into clinical practice.

Limitations

The study was conducted at a single center, limiting the sample size, which was considered the most critical limitation.

Conclusion

Cervical cancer needs prognostic markers and algorithms for both early diagnosis and diagnosis, as well as treatment and surveillance. This study will serve as a guide for future research.

References

1. Gennigens C, De Cuyper M, Hermesse J, Kridelka F, Jerusalem G. Optimal treatment in locally advanced cervical cancer. *Expert Rev Anticancer Ther.* 2021;21(6):657-71. doi:10.1080/14737140.2021.1879646.
2. Olawaiye AB, Baker TP, Washington MK, Mutch DG. The new (Version 9) American Joint Committee on Cancer tumor, node, metastasis staging for cervical cancer. *CA Cancer J Clin.* 2021;71(4):287-98. doi:10.3322/caac.21663.

3. Adam JA, Poel E, van Eck-Smit BLF, et al. Lymphatic mapping for image-guided radiotherapy in patients with locally advanced uterine cervical cancer: a feasibility study. *EJNMMI Res.* 2023;13(1):58. doi:10.1186/s13550-023-00989-0.
4. Abu-Rustum NR, Yashar CM, Arend R, et al. NCCN Guidelines® insights: cervical cancer, version 1.2024. *J Natl Compr Canc Netw.* 2023;21(12):1224-33. doi:10.6004/jnccn.2023.0062.
5. Pinto PJJ, Chen MJ, Santos Neto E, et al. Prognostic factors in locally advanced cervical cancer with pelvic lymph node metastasis. *Int J Gynecol Cancer.* 2022;32(3):239-45. doi:10.1136/ijgc-2021-003140.
6. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer.* 2005;104(6):1129-37. doi:10.1002/cncr.21324.
7. Mabuchi S, Komura N, Kodama M, Maeda M, Matsumoto Y, Kamiura S. Significance of the number and the location of metastatic lymph nodes in locally recurrent or persistent cervical cancer patients treated with salvage hysterectomy plus lymphadenectomy. *Curr Oncol.* 2022;29(7):4856-67. doi:10.3390/curroncol29070385.
8. Mestdagh F, Steyaert A, Lavand'homme P. Cancer pain management: a narrative review of current concepts, strategies, and techniques. *Curr Oncol.* 2023;30(7):6838-58. doi:10.3390/curroncol30070500.
9. Zhang X, Zhang Q, Xie L, et al. The value of whole-tumor texture analysis of ADC in predicting the early recurrence of locally advanced cervical squamous cell cancer treated with concurrent chemoradiotherapy. *Front Oncol.* 2022;12:852308. doi:10.3389/fonc.2022.852308.
10. Jiang P, Kong W, Gong C, et al. Predicting the recurrence of operable cervical cancer patients based on hemoglobin, albumin, lymphocyte, and platelet (HALP) score and classical clinicopathological parameters. *J Inflamm Res.* 2022;15:5265-81. doi:10.2147/JIR.S383742.
11. Kirkwood JM, Tarhini A, Sparano JA, et al. Comparative clinical benefits of systemic adjuvant therapy for paradigm solid tumors. *Cancer Treat Rev.* 2012;39(1):27-43. doi:10.1016/j.ctrv.2012.03.007.
12. Vittrup AS, Kirchheiner K, Pötter R, et al. Overall severe morbidity after chemoradiation therapy and magnetic resonance imaging-guided adaptive brachytherapy in locally advanced cervical cancer: results from the EMBRACE-I study. *Int J Radiat Oncol Biol Phys.* 2023;116(4):807-24. doi:10.1016/j.jrobp.2023.01.002.
13. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol.* 2008;26(35):5802-12. doi:10.1200/JCO.2008.16.4368.
14. de la Torre M. Neoadjuvant chemotherapy in women with early or locally advanced cervical cancer. *Rep Pract Oncol Radiother.* 2018;23(6):528-32. doi:10.1016/j.rpor.2018.09.005.
15. Ramirez PT, Robledo KP, Frumovitz M, et al. LACC trial: final analysis on overall survival comparing open versus minimally invasive radical hysterectomy for early-stage cervical cancer. *J Clin Oncol.* 2024;42(23):2741-6. doi:10.1200/JCO.23.02335.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Availability Statement

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Declarations

This study was approved by the Ethics Committee of Selçuk University (Date: 2025-01-14, No: E922332)

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